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The Mannich aminomethylation reaction of aromatic thiols has been used to produce diaza-18-crown-6 ligands containing thiol-derived side arms. Thiophenols were attached to the azacrown through N-CH_2-S linkages even in the presence of hydroxy or acetamido groups. Heteroaromatic thiols containing N=C-SH (or NH-C=S) structural fragments were attached to diaza-18-crown-6 by N-CH_2-N linkages with the thiol becoming a thione function. X-ray crystal structures provide proof of the N-CH_2-S and N-CH_2-N linkages for the products of reactions with thiophenols and heteroaromatic thiols, respectively.

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by

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SYNTHESES AND CRYSTAL STRUCTURES OF NOVEL DIAZA-18-CROWN-6 LIGANDS CONTAINING AROMATIC THIOL-DERIVED ARMS

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Attachment of metal-ion chelating groups to macrocyclic ligands has yielded compounds with marked improvements in ligating properties over the parent macrocyclic ligands. In this context, we recently reported that 5-chloro-8-hydroxyquinoline (CHQ)-substituted diaza-18-crown-6 ligands (**1** and **2**, Figure 1) showed greatly improved ion-complexing ability and selectivity for certain metal ions compared to unsubstituted diaza-18-crown-6 [1,2]. For example, the log *K* value for the **2**-Ba^{2+} complex (log *K* = 12.2, in methanol) is in the same magnitude as that of the cryptand [2.2.2]-Ba^{2+} complex. Indeed, **2** forms a pseudocryptand through π-π interaction between the CHQ rings when complexed with Ba^{2+} and all 10 donor atoms of **2** are involved in coordination as shown by the ^{1}H nmr spectrum and an X-ray crystal structure [1]. *o*-Aminophenol-substituted diaza-18-crown-6 ligands (**3** and **4**) have been shown to function as heterobinuclear receptors for Cu^{2+} and Na^+ [3]. When solutions of **3**-Cu^{2+} and **4**-Cu^{2+} were titrated by a Na^+ solution, appreciable interactions of Na^+ with **3**-Cu^{2+} and **4**-Cu^{2+} were observed as shown by log *K* values (1.41 and 1.86, respectively).

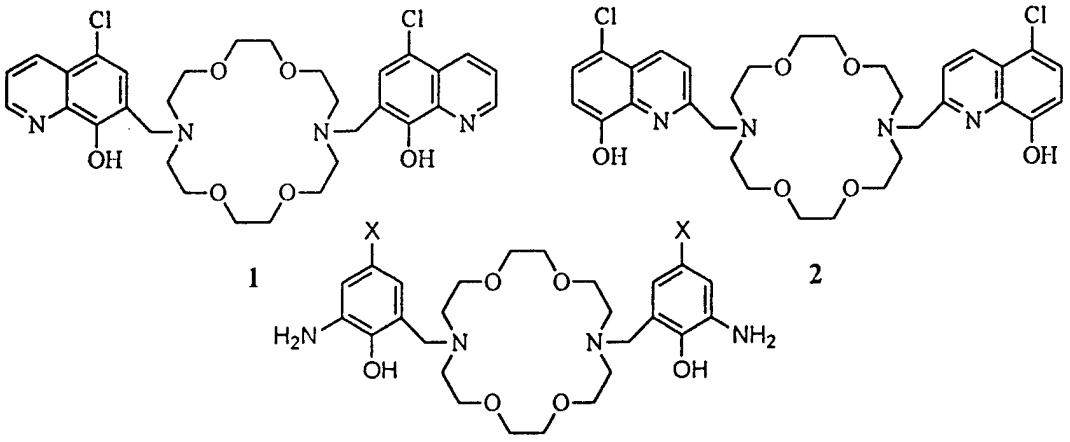
We now report the syntheses of ten diaza-18-crown-6 ligands having two sulfur-containing aromatic side arms. Since sulfur interacts strongly with soft metal ions, we expect these ligands to selectively bind transition and post-transition metal ions. X-ray crystal structures of four of these ligands with aromatic substituents attached through an N-CH_2-S linkage and heteroaromatic substituents attached through N-CH_2-N linkages are described.

Thiols have been used as reactants in the Mannich reaction [4], and in the presence of an aldehyde or a ketone, thiols condense with primary amines [5], secondary amines [6], hydroxylamine [7], primary and secondary amides [8], amino acids [9], or ammonia [10] leading to the formation of compounds containing N-CH_2-S linkages. Depending on the number of hydrogens on the nitrogen atom and the ratio of starting materials, one, two or three thiol units can be attached to the same nitrogen atom. For example, secondary amines condense with one equivalent of thiol to give R-S-CH_2-NR'_2 groups.

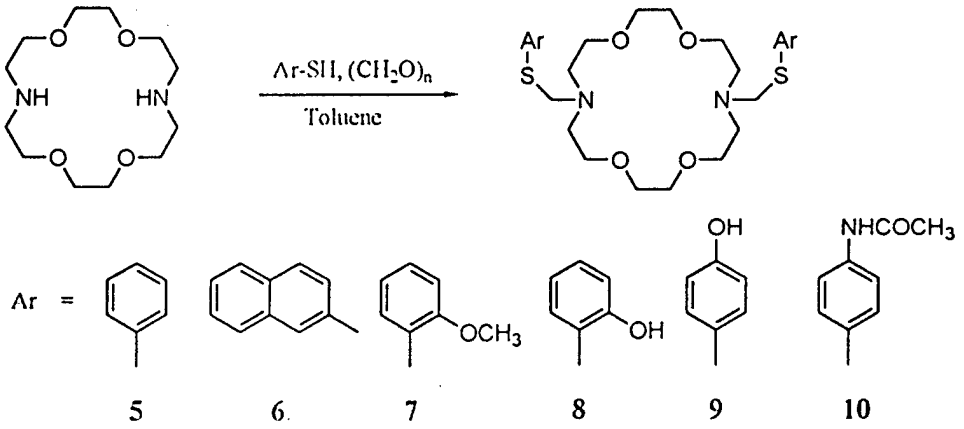
We have used the Mannich aminomethylation reaction with thiols and diazacrown ether to form azacrown ether ligands containing two thiol-derived side arms. The classical Mannich condensation reaction uses amines, formaldehyde and an appropriate receptor for aminomethylation and is usually conducted in polar solvents such as an alcohol, formic acid, or dimethylformamide [11]. In this study, we used solid paraformaldehyde instead of a formaldehye solution and performed the Mannich reaction with the thiols in toluene [12]. The one-pot Mannich reaction gave all aromatic thiol-derived diaza-18-crown-6 ligands (**5**-**14**, Schemes 1 & 2) in good yields [13]. All compounds were purified by sonication in a small amount of methyl alcohol followed by filtration and drying.

For the thiophenols, N-CH_2-S linkages were formed exclusively (**5**-**10**, Scheme 1). The exclusive formation of **8** and **9** from the corresponding hydroxythiophenols is somewhat surprising, since phenol is well known for its ability to direct aminomethylation to form a proton-ionizable *ortho* or *para* substituted phenol-containing azacrown ether [14]. The exclusive formation of **10** is also interesting because an amide nitrogen is also capable of undergoing the Mannich reaction to form an N-CH_2-N linkage [14].

Figure 1. Compounds mentioned in the Introduction.



Scheme 1. The syntheses of new thiophenol-derived diaza-18-crown-6 ligands with N-CH_2-S linkages



Scheme 2. The synthesis of new heteroaromatic thiol-derived azacrown ether ligands with N-CH_2-N linkages

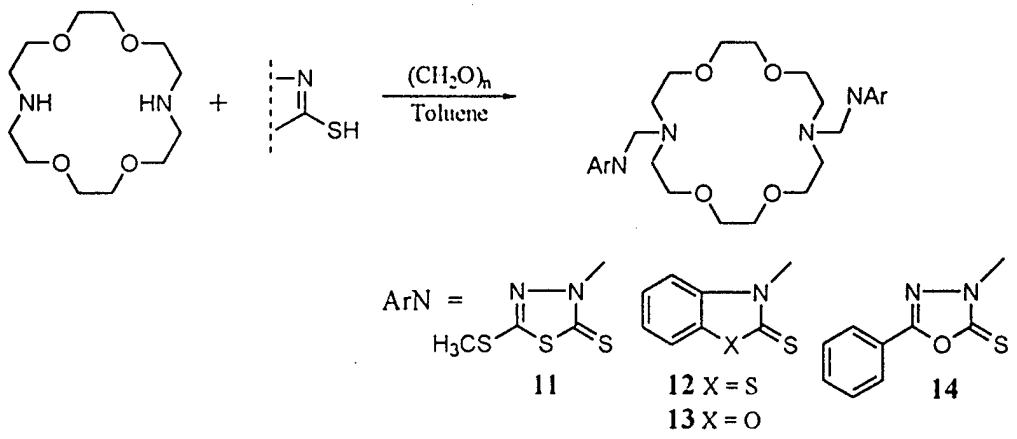


Table 1

Summary of δ_H , δ_C (ppm, in dimethylsulfoxide-d_6) and Selected Bond Length (Å) Data of N-CH_2-S and N-CH_2-N Linkages.

Ligands	δ_H	δ_C	C6-S7
5	4.62	69.73	N/A
6	4.75	69.70	N/A
7	4.52	69.72	N/A
8	4.44	69.73	1.770(5)
9	4.43	69.74	N/A
10	4.54	69.72	N/A
Average	4.55	69.72	1.770
Ligands	δ_H	δ_C	C1-S1
11	5.22	69.92	1.665(4)
12	5.32	70.03	1.656(3)
13	5.17	69.99	1.644(2)
14	5.14	69.91	N/A
Average	5.21	69.96	1.655

For heteroaromatic thiols containing N=C-SH structural fragments, the Mannich reaction with diaza-18-crown-6 gave ligands **11-14** (Scheme 2) which contain the N-CH_2-N linkage. In this case, no products with N-CH_2-S linkages were observed.

The formation of distinctive N-CH_2-S linkages from the thiophenols and N-CH_2-N linkages from the heteroaromatic thiols is further confirmed by the proton nmr spectra of the products. There are significant differences in chemical shifts of the proton signals for -CH_2- groups among the various thiol-derived products (Table 1). The average chemical shift of the signal for -CH_2- in N-CH_2-S linkages of **5-10** is 0.66 ppm upfield in the ^{1}H nmr spectra and 0.24 ppm upfield in the ^{13}C nmr spectra from that of the -CH_2- in N-CH_2-N linkages of **11-14**. In addition, the two types of linkages can be observed by X-ray crystallography. The crystal structures of **8, 11, 12,** and **13** were shown in Figures 2-5, respectively. Selected bond lengths of C6-S7 of **8** and C1-S1 of **11-13** are also shown in Table 1. The C1-S1 bond is about 0.12 Å shorter than the C6-S7 bond.

EXPERIMENTAL

The ^{1}H nmr spectra (300 MHz) and ^{13}C nmr spectra (75 MHz) were recorded in dimethylsulfoxide-d_6. Solvents and starting materials were purchased from commercial sources where available.

General Procedure for the Syntheses of Compounds 5-14 Using the One-Pot Mannich Reaction (Schemes 1 & 2). An anhydrous toluene solution (180 ml) of 4,13-diaza-18-crown-6 (1.00 g, 3.82 mmoles), paraformaldehyde (280 mg, 9.30 mmoles), and

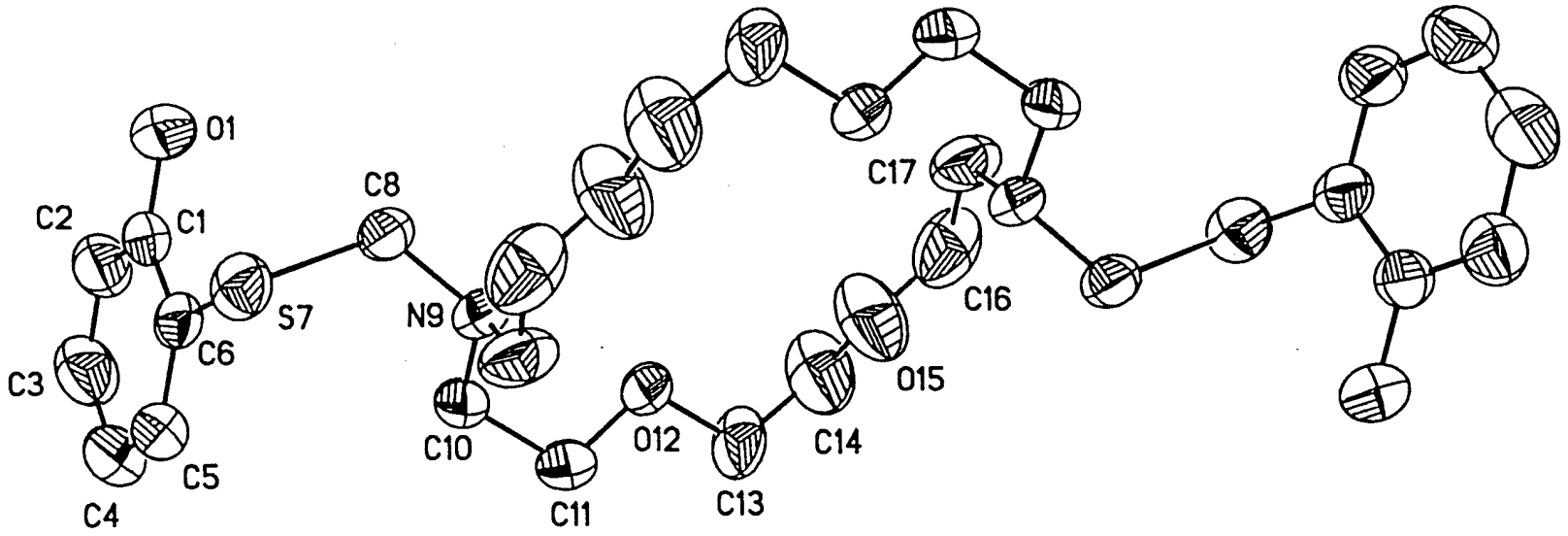


Figure 2. The solid state structure of 8. The hydrogen atoms and C16' were omitted for clarity.

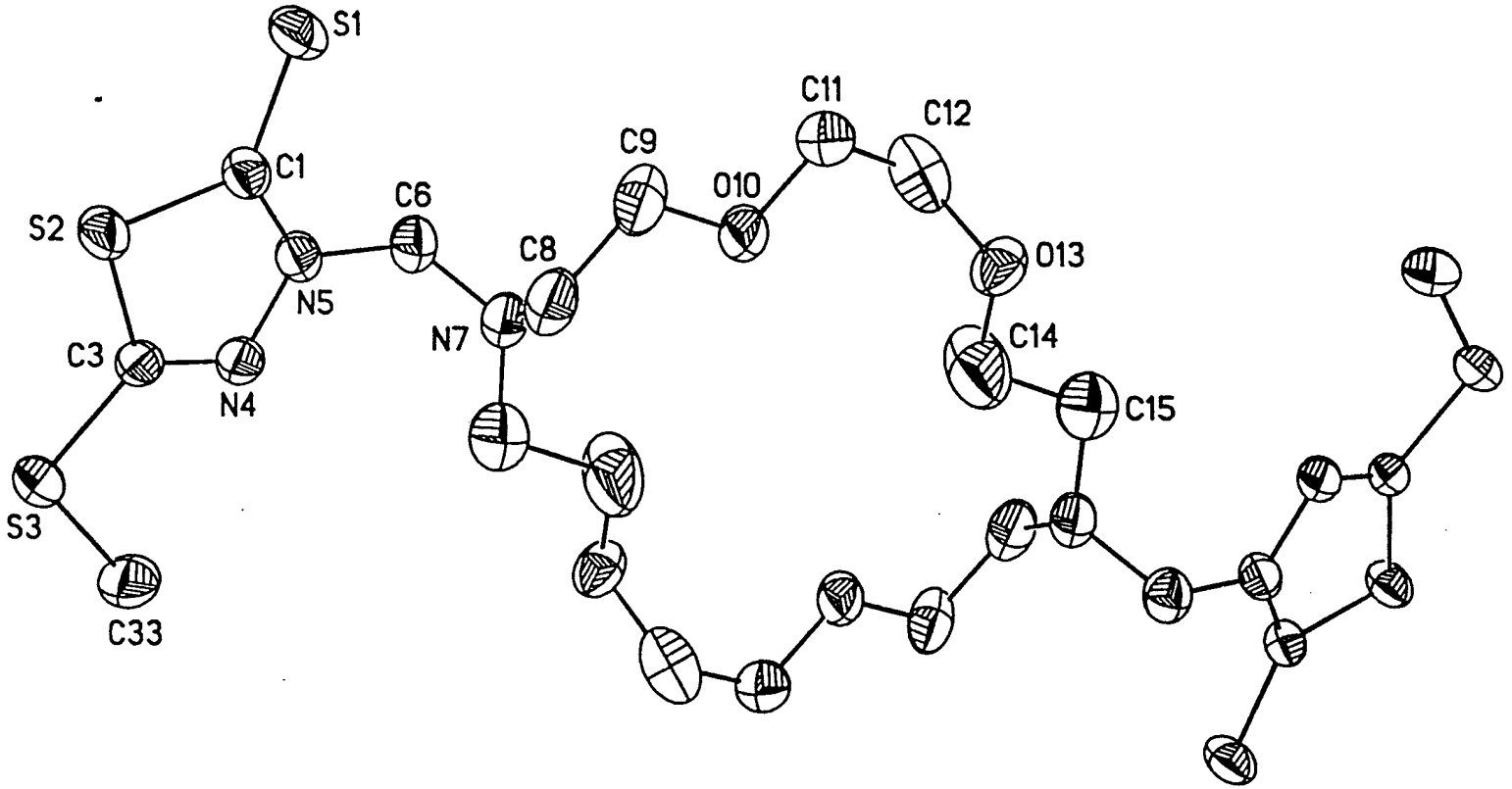


Figure 3. The solid state structure of **11**. The hydrogen atoms and C14' were omitted for clarity.

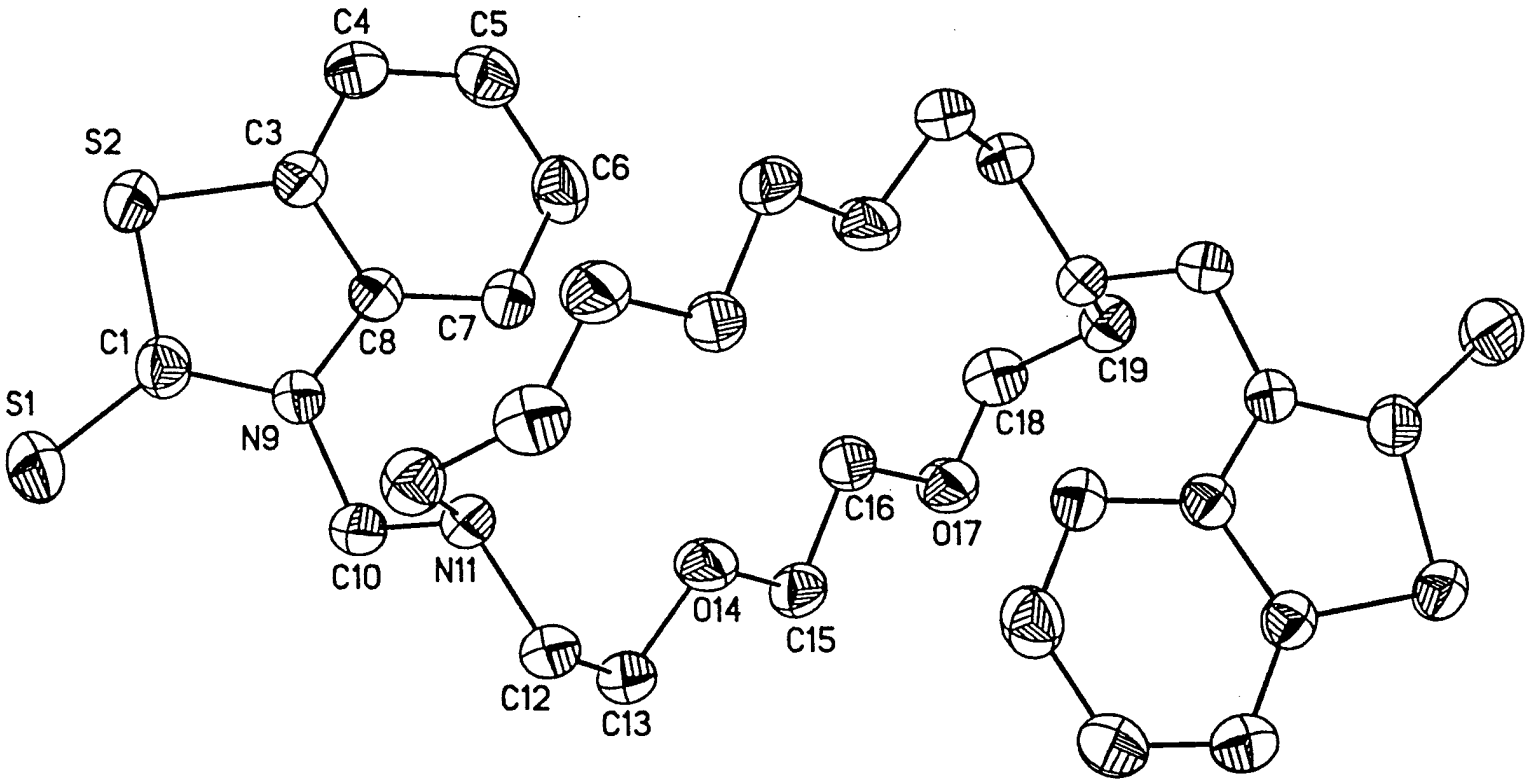


Figure 4. The solid state structure of **12**. The hydrogen atoms were omitted for clarity.

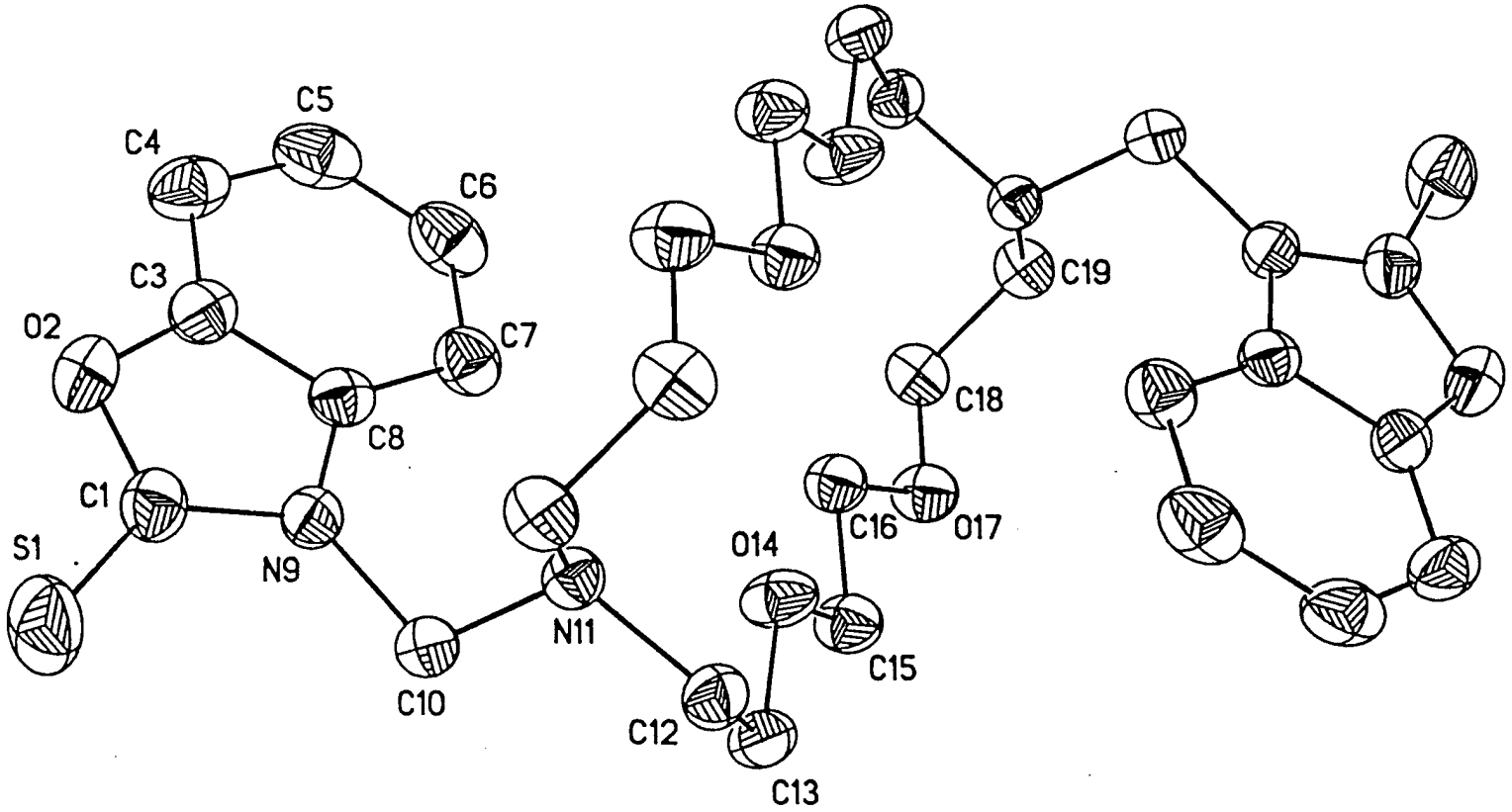


Figure 5. The solid state structure of 13. The hydrogen atoms were omitted for clarity.

the appropriate aromatic thiol (8.40 mmoles) was refluxed for 20 hours. The solvent was evaporated under reduced pressure, and a small amount of methanol was added. The mixture was sonicated for 20 to 30 minutes. The resulting solid was collected by filtration and dried.

7,16-Bis(phenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (5). Ligand **5** (0.95 g, 49%) was prepared from thiophenol to give a white solid, mp 97-98°; ^{1}H nmr δ: 2.73 (t, J = 5.4 Hz, 8H), 3.44 (m, 16H), 4.62 (s, 4H), 7.20 (m, 2H), 7.29 (m, 4H), 7.45 (m, 4H); ^{13}C nmr δ: 52.20, 65.19, 68.82, 69.73, 126.71, 128.96, 131.21, 137.39. *Anal.* Calcd. for $C_{26}H_{38}N_2O_4S_2$: C, 61.63; H, 7.56. Found: C, 61.59; H, 7.59.

7,16-Bis(2-naphthylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (6). Ligand **6** (1.25 g, 54%) was prepared from 2-thionaphthol to give a white solid, mp 112-113°; ^{1}H nmr δ: 2.76 (t, J = 5.5 Hz, 8H), 3.42 (s, 16H), 4.75 (s, 4H), 7.50 (m, 6H), 7.83 (m, 6H), 8.00 (s, 2H); ^{13}C nmr δ: 52.26, 64.99, 68.86, 69.70, 125.72, 126.53, 126.95, 127.55, 128.22, 128.82, 129.07, 131.29, 133.40, 135.05. *Anal.* Calcd. for $C_{34}H_{42}N_2O_4S_2$: C, 67.29; H, 6.98. Found: C, 67.05; H, 6.82.

7,16-Bis(2-methoxyphenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (7). Ligand **7** (0.95 g, 44%) was prepared from 2-methoxythiophenol to give a white solid, mp 84-86°; ^{1}H nmr δ: 2.73 (t, J = 5.5 Hz, 8H), 3.44 (s, 16H), 3.82 (s, 6H), 4.52 (s, 4H), 6.88 (t, J = 7.6 Hz, 2H), 6.98 (d, J = 8.3 Hz, 2H), 7.22 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H); ^{13}C nmr δ: 52.14, 55.61, 63.14, 68.83, 69.72, 111.22, 120.83, 124.50, 127.90, 132.59, 158.05. *Anal.* Calcd. for $C_{28}H_{42}N_2O_6S_2$: C, 59.34; H, 7.47. Found: C, 59.06; H, 7.43.

7,16-Bis(2-hydroxyphenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (8). Ligand **8** (1.21 g, 59%) was prepared from 2-hydroxythiophenol to give a light yellow solid, mp 87-88°; ^{1}H nmr δ: 2.76 (t, J = 5.4 Hz, 8H), 3.43 (s, 16H), 4.44 (s, 4H), 6.72 (td, J = 1.2, 7.6 Hz, 2H), 6.82 (dd, J = 1.0, 8.1 Hz, 2H), 7.07 (td, J = 1.5, 8.1 Hz, 2H), 7.34 (dd, J = 1.5, 7.6 Hz, 2H), 9.87 (br s, 2H); ^{13}C nmr δ: 52.04, 63.38, 68.71, 69.73, 115.51, 119.46, 121.86, 128.34, 133.81, 157.16. *Anal.* Calcd. for $C_{26}H_{38}N_2O_6S_2$: C, 57.97; H, 7.11. Found: C, 58.06; H, 7.27.

7,16-Bis(4-hydroxyphenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (9). Ligand **9** (1.38 g, 67%) was prepared from 4-hydroxythiophenol to give a light yellow solid, mp 160-161°; ^{1}H nmr δ: 2.72 (t, J = 5.6 Hz, 8H), 3.43 (m, 16H), 4.43 (s, 4H), 6.70 (dt, J = 2.9, 8.5 Hz, 4H), 7.28 (dt, J = 2.9, 8.5 Hz, 4H), 9.55 (br s, 2H); ^{13}C nmr δ: 52.22, 66.64, 68.81, 69.74, 116.08, 125.14, 134.62, 156.70. *Anal.* Calcd. for $C_{26}H_{38}N_2O_6S_2$: C, 57.97; H, 7.11. Found: C, 58.01; H, 6.96.

7,16-Bis(4-acetamidophenylthiomethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (10). Ligand **10** (1.37 g, 58%) was prepared from 4-acetamidothiophenol to give a white solid, mp 175-176°; ^{1}H nmr δ: 2.03 (s, 6H), 2.71 (t, J = 5.4 Hz, 8H), 3.59 (t, J = 5.4 Hz, 8H), 3.43 (s, 8H), 4.54 (s, 4H), 7.38 (d, J = 8.5 Hz, 4H), 7.51 (d, J = 8.5 Hz, 4H), 9.96 (s, 2H); ^{13}C nmr δ: 24.00, 52.18, 65.99, 68.79, 69.72,

119.44, 130.44, 132.62, 138.01, 168.25. *Anal.* Calcd. for $C_{30}H_{44}N_4O_6S_2$: C, 58.04; H, 7.14. Found: C, 58.07; H, 6.94.

7,16-Bis(5-methylthio-1,3,4-thiadiazole-2-thione-3-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (11). Ligand **11** (1.23 g, 52%) was prepared from 5-methylthio-1,3,4-thiadiazole-2-thiol to give a white solid, mp 110-112°; ^{1}H nmr δ: 2.64 (s, 6H), 2.98 (br s, 8H), 3.52 (m, 8H), 5.22 (s, 4H); ^{13}C nmr δ: 15.48, 51.92, 69.26, 69.62, 69.92, 156.94, 185.91. *Anal.* Calcd. for $C_{20}H_{34}N_4O_6S_6$: C, 38.81; H, 5.54. Found: C, 39.10; H, 5.48.

7,16-Bis(benzothiazole-2-thione-3-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (12). Ligand **12** (0.85 g, 36%) was prepared from 2-mercaptobenzothiazole to give a light yellow solid, mp 152-154°; ^{1}H nmr δ: 2.94 (br s, 8H), 3.47 (m, 16H), 5.32 (s, 4H), 7.30 (t, J = 7.6 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 7.8 Hz, 2H); ^{13}C nmr δ: 51.64, 65.66, 69.08, 70.03, 114.43, 121.29, 124.99, 126.71, 127.21, 142.74, 163.20. *Anal.* Calcd. for $C_{28}H_{36}N_4O_4S_4$: C, 54.17; H, 5.84. Found: C, 54.19; H, 5.77.

7,16-Bis(benzoxazole-2-thione-3-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (13). Ligand **13** (1.18 g, 53%) was prepared from 2-mercaptobenzoxazole to give a white solid, mp 153-155°; ^{1}H nmr δ: 2.95 (t, J = 5.4 Hz, 8H), 3.43 (s, 8H), 3.51 (t, J = 5.4 Hz, 8H), 5.17 (s, 4H), 7.30 (m, 4H), 7.52 (m, 4H); ^{13}C nmr δ: 51.94, 66.88, 69.17, 69.99, 109.79, 112.10, 124.07, 124.83, 132.15, 146.67, 180.07. *Anal.* Calcd. for $C_{28}H_{36}N_4O_6S_2$: C, 57.12; H, 6.16. Found: C, 57.34; H, 6.31.

7,16-Bis(5-phenyl-1,3,4-oxadiazole-2-thione-3-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (14). Ligand **14** (1.13 g, 46%) was prepared from 5-phenyl-1,3,4-oxadiazole-2-thiol to give a white solid, mp 156-157°; ^{1}H nmr δ: 3.02 (t, J = 5.4 Hz, 8H), 3.54 (s, 8H), 3.58 (t, J = 5.4 Hz, 8H), 5.14 (s, 4H), 7.60 (m, 6H), 7.89 (m, 4H); ^{13}C nmr δ: 51.75, 69.15, 69.33, 69.91, 122.39, 126.11, 132.28, 158.75, 177.05. *Anal.* Calcd. for $C_{30}H_{38}N_6O_6S_2$: C, 56.06; H, 5.96. Found: C, 55.96; H, 5.96.

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